Technology to Help Diabetics

WHEN the 7-year-old daughter of a Livermore physicist was diagnosed with diabetes in 1994, her doctor at Stanford Children's Hospital, Dr. Darrell Wilson, happened to be familiar with the Laboratory. Wilson's father-in-law was Carl Haussmann, one of the Laboratory's founders (see *S&TR*, January/February 2000), so over the years, he had heard about the unique technological capabilities of the Laboratory. He suggested that Livermore might be able to do something for the sufferers of diabetes.

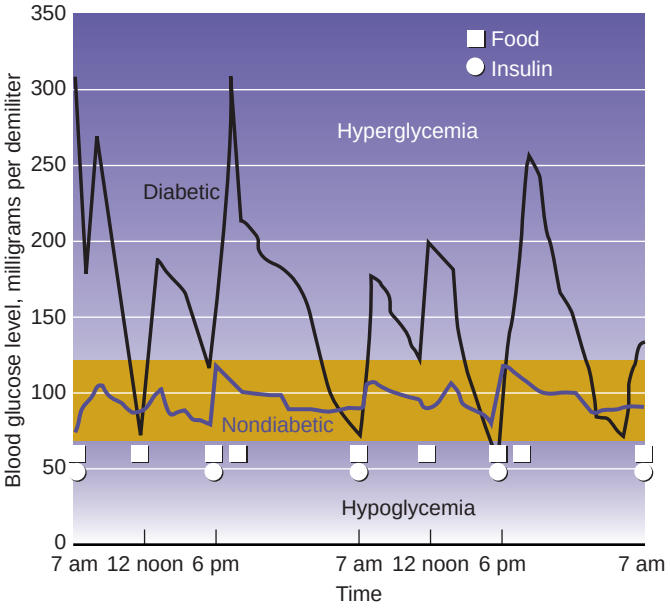
It was a chance remark, one that might have gone nowhere. But the physicist, Tom Peyser of the Defense and Nuclear Technologies Directorate, saw that he could tap into Livermore's growing capability in medical technologies, a field that combines expertise in chemistry, physics, optics, electronics, and microfabrication. He and fellow physicist Steve Lane took up Dr. Wilson's challenge and began a systematic examination of the technology necessary for continuous monitoring of blood sugar in diabetics. Many private companies already were working on this problem, but Peyser and Lane thought that the Laboratory was uniquely situated to tackle the problem using optical technologies. They also realized that spinoffs from their work on glucose sensors might benefit other Laboratory missions, such as programs for detecting hostile chemical and biological agents.

Diabetic Jenny Peyser, now 14 years old, and her father, Livermore physicist Tom Peyser. (Photo taken by freelance photographer Margaret Kaye.)

Work on the glucose sensor began in 1995 when the Livermore project team linked up with MiniMed, Inc., of Northridge, California, to develop an optochemical glucose sensor. The project has received grants from the Laboratory Directed Research and Development Program and subsequently been funded by the National Institutes of Health and the Department of Commerce's Advanced Technology Program.

MiniMed is the largest supplier of insulin pumps, small pager-size programmable medical devices that administer insulin to diabetics in place of multiple daily injections. Someday, the Livermore–MiniMed sensor may be combined with a MiniMed insulin pump to create an artificial pancreas, which could change the lives of millions of diabetics.

Diabetes is a metabolic disease in which the body does not produce or use insulin properly. Insulin is a hormone secreted by the pancreas that allows glucose, the energy source for the cells in our body, to enter the cells. Careful stabilization of glucose levels is crucial for diabetics to avoid a host of complications. Long-term high glucose levels, or hyperglycemia, may lead to heart disease, hypertension, blindness, stroke, kidney failure, and amputations. In fact, complications from diabetes are the leading cause of blindness, kidney failure, and amputations in the U.S. Hypoglycemia, or low glucose levels, can lead to unconsciousness and death. The direct and indirect costs of diabetes to the U.S. health care system exceed $100 billion annually.



Blood glucose levels for nondiabetic and insulin-dependent diabetic subjects. Even with regular insulin injections, diabetics using current treatment methods are unable to mimic normal control of glucose levels.

Diabetic patients must test their blood sugar daily. Some patients have to test themselves up to eight or more times a day. They prick a finger to draw blood for reading by a handheld blood glucose meter, and then they inject the necessary amount of insulin determined by the meter reading. Because of the pain and inconvenience of the testing, many patients do not monitor their glucose as often as they should. What's more, even if they do test themselves regularly, current technologies make it virtually impossible to test often enough to maintain reasonably stable glucose levels. The new sensor that Livermore and MiniMed are developing can be implanted under the skin without surgery and is expected to last for a year before replacement. "We're still in the early developmental stages with the sensor," says Lane, associate program leader for Livermore's Medical Technology Program. "It will probably be several years before it hits the market."

Livermore's work on this project has not gone unnoticed. At a White House ceremony in January, the Department of Energy awarded one of five Bright Light Awards to the Livermore team for consumer-oriented innovation. In May, the Federal Laboratory Consortium honored Livermore with an Excellence in Technology Transfer Award for transferring the glucose monitoring technology to a private-sector company.

Fluorescence Tells the Story

The new device is a small disk with a fluorescent chemical sensor that consists of engineered molecules embedded within a polymer. In the absence of glucose, the sensor's molecules have a low level of fluorescence. The presence of glucose alters the molecules' electron configuration so they become much more fluorescent and emit light of a specific color. If developmental work on the device goes as planned, a small handheld instrument will shine light on the skin, and a small detector will measure the resulting fluorescence. The intensity, or brightness, of this emitted fluorescence will allow the body's glucose level to be determined. A more intense light emission corresponds to a higher glucose level.

An alternative approach is also being developed in which the fluorescent lifetimes of the molecules are measured by the instrument. Sensor molecules bound to glucose have longer fluorescent lifetimes than molecules that are not bound. The average lifetime can therefore be used to determine the

glucose level. This method is much more tolerant to instrument and other errors. Even something as mundane as moving the place where a patient wears a watch can change the detector's readings using the first method.

The first step in developing the sensor was to demonstrate that it was possible to receive a signal from a fluorescent sample placed under the skin. A beam from a light-emitting diode was passed through a fiber-optic line to the surface of the skin, through the skin to the fluorescent-doped plastic, and back out of a fiber-optic line to a spectrometer that measured the intensity of the fluorescence. This demonstrated that transdermal fluorescent signaling was possible. But it also pointed out that only long-wavelength light can easily pass through skin and other tissue (as demonstrated when only red light from a white flashlight beam shines through the hand).

The Right Fluorescence Molecules

Following earlier work by a Japanese group, several Livermore chemists led by Joe Satcher, working with researchers from MiniMed, designed switchable anthracene boronate (AB) molecules, or fluorophores. The AB molecules are weak fluorescers when not bound to glucose but become bright when they are. Next, Livermore developed "linkers" that could be synthetically attached to the AB molecules so that the molecules could, in turn, be attached to a biocompatible polymer substrate. Finally, the team screened a large number of candidate polymers to hold the AB fluorophores. They found a pHEMA (polyhydroxyethyl methacrylate) blend, a material similar to that used for contact lenses. This material is strong and sufficiently permeable to allow glucose to enter, does not irritate the skin, and allows the AB molecules to function properly even when they are covalently bonded to the polymer.

At the West Los Angeles Veterans Administration Hospital, Livermore and MiniMed first demonstrated the glucose-sensitive fluorescent implant in the ear of an anesthetized rat. The fluorescence signal closely tracked a separate independent measurement of the rat's glucose levels as the animal's blood sugar was raised and lowered over a 2- to 3-hour period. In these tests, the implant remained operational for two weeks, the duration of the experiment.

Challenges remain to fully developing the sensor. "The biggest hurdle right now," says Lane, "is engineering a fluorophor with a wavelength that is long enough to be reliably detected through the skin."

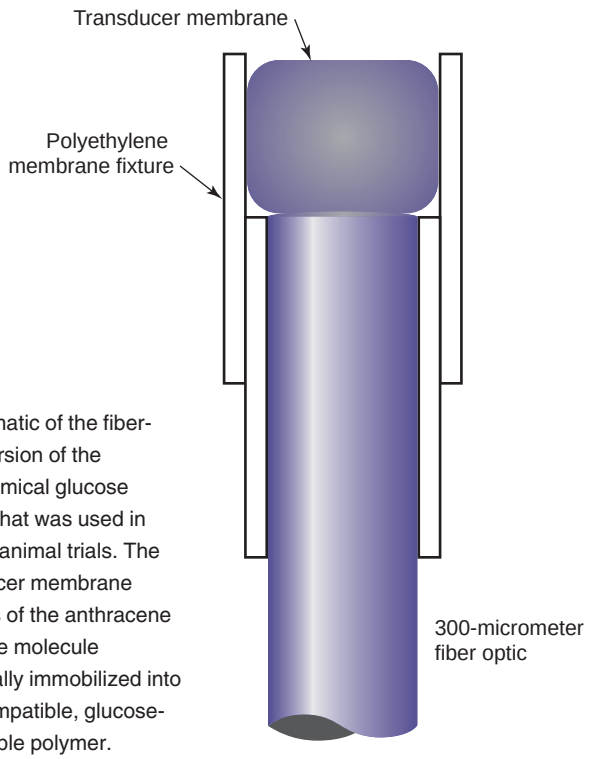
The AB molecule absorbs light at 380 nanometers and emits fluorescent light at 420 nanometers. Recently, new glucose-sensitive fluorescent compounds have been synthesized and tested at Livermore and MiniMed that absorb red light at 620 nanometers and emit at 670 nanometers. "If these molecules can be made to mimic the other properties of AB, our job will be nearly complete," adds Lane.

The team has also developed an alternate method that has been tested on rats. In this version, a sensor membrane was fixed onto the end of an optical fiber and then inserted under the skin of the animal where it remained for many hours. Light at one wavelength was sent down the optical fiber from outside the animal's body. The sensor gave off fluorescence of an intensity duration that depended on the concentration of glucose in the surrounding tissue. The fluorescent light

Steve Lane takes a glucose-sensitive fluorescent polymer out of a glass vial for observation.

emitted by the sensor was at a different wavelength than the incoming light; it traveled back up the optical fiber where it was measured by a detector outside the body. The glucose levels in the tissue could then be read via the fiber-optic cable rather than via light transmitted directly through the skin. In this case, long-wavelength fluorescence is not necessary.

As they continue to pursue the transdermal sensor, Livermore and MiniMed are also furthering the development of the fiber-optic version, which would be implanted under the skin using a needle. A similar electrochemical glucose sensor already marketed by MiniMed is implanted the same way.



A schematic of the fiber-optic version of the optochemical glucose sensor that was used in the first animal trials. The transducer membrane consists of the anthracene boronate molecule chemically immobilized into a biocompatible, glucose-permeable polymer.

Livermore may be able to exploit the research on fluorescent molecules in its effort to develop sensors to detect biological agents of terrorism as well as for a range of other biomedical applications. Knowledge gained in the process of developing the glucose sensor may lead to methods for detecting small amounts of a deadly toxin or pathogen.

The Search for a Solution

Livermore and MiniMed are not the only ones trying to achieve a reliable glucose sensor for diabetes patients. For 30 years, researchers have been trying to solve the puzzle of long-term glucose sensing. Lane estimates that work is under way in at least 100 public- and private-sector laboratories worldwide to produce a continuously operating glucose sensor. With millions of sufferers and billions of dollars spent annually to treat the disease, a solution to this problem is urgently needed.

Peyser says, “We have a long way to go before making a product, but we have taken the first steps and have measured glucose in animals using this fluorescent technique. We’re at a point similar to that of the Wright brothers flying their first airplane a few hundred feet. We’ve established that fluorescent glucose sensors are feasible.” The Livermore team is hoping that progress on the long-wavelength compound and on the polymer work will allow resumption of animal tests in the near future. When those tests are completed, MiniMed will likely begin the next phase of research and development, namely, rigorously conducted clinical trials supervised by the Food and Drug Administration. It is a lengthy and costly process, but if Livermore and MiniMed succeed in combining their glucose sensor with an insulin pump, diabetes patients everywhere will applaud.

—Katie Walter

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